Journal of biological chemistry (United States) Jul 13 2001, 276 (28) p25742-52, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: DK 25541; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Sodium butyrate, an erythroid differentiation inducer and a **histone deacetylase** inhibitor, increases G alpha(i2) levels in differentiating K562 cells. Here we show that sodium butyrate induces G alpha(i2) gene transcription via sequences at -50/-36 and -92/-85 in the G alpha(i2) gene promoter. Both sequences contain core sequence motif for Sp1 binding; electrophoretic mobility shift as well as supershift assays confirmed binding to Sp1. Transcription from the G alpha(i2) gene promoter was also activated by two other **histone deacetylase** inhibitors, trichostatin A and Helminthsporium carbonium toxin (HC toxin), which also induce erythroblastic differentiation in K562 cells. However, hydroxyurea, a potent erythroid differentiation inducer in these cells, did not activate transcription from this gene promoter, indicating that promoter activation is inducer-specific. Mutations within the Sp1 sites at -50/-36 and -92/-85 in the G alpha(i2) gene promoter substantially decreased transcriptional activation by sodium butyrate, trichostatin A, or HC toxin. Transfection with constitutively activated ERKs indicated that this promoter can be activated through the MEK-ERK signal transduction pathway. Inhibition of the MEK-ERK pathway with U0126 or reduction in the expression of endogenous ERK with an **antisense** oligonucleotide to ERK significantly inhibited sodium butyrate- and HC toxin-induced transcription but had no effect on trichostatin A-induced transcription. Inhibition of the JNK and p38 MAPKs, using selective inhibitors, had no effect on sodium butyrate-induced transcription. In cells in which sodium butyrate induction of promoter activation had been inhibited by various concentrations of U0126, constitutively activated ERK2 reversed this inhibition. These results show that the MEK-ERK signal transduction pathway is important in butyrate signaling, which eventually converges in the cell nucleus.

3/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11270202 21301568 PMID: 11408941

Evidence of a functional role for the cyclin-dependent kinase-inhibitor p21WAF1/CIP1/MDA6 in promoting differentiation and preventing mitochondrial dysfunction and apoptosis induced by sodium butyrate in human myelomonocytic leukemia cells (U937).

Rosato R R; Wang Z; Gopalkrishnan R V; Fisher P B; Grant S
Department of Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298, USA.

International journal of oncology (Greece) Jul 2001, 19 (1) p181-91, ISSN 1019-6439 Journal Code: 9306042
Contract/Grant No.: CA 35675; CA; NCI; CA 63753; CA; NCI; CA 74468; CA; NCI; CA 83705; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The impact of dysregulation of the cyclin-dependent kinase inhibitor p21WAF1/CIP1/MDA6 has been examined in U937 human monocytic leukemia cells in relation to cell cycle arrest and differentiation following treatment with the **histone deacetylase** inhibitor sodium butyrate (SB). Cells stably transfected with a p21WAF1/CIP1/MDA6 **antisense** construct, in marked contrast to their wild-type counterparts, failed to up-regulate p21WAF1/CIP1/MDA6, undergo G1 arrest, or express the maturation marker CD11b when exposed to 1 or 3 mM SB. However, **antisense** -expressing cells were significantly more susceptible to SB-mediated

mitochondrial injury and apoptosis, manifested by increased cytosolic translocation of cytochrome c, activation of pro-caspase 3, and degradation of PARP. Dysregulation of p21WAF1/CIP1/MDA6 did not modify the extent of SB-induced **histone** acetylation, but did result in cleavage of p27KIP1, Bcl-2 and pRb, as well as diminished levels of full-length underphosphorylated pRb. Finally, dysregulation of p21WAF1/CIP1/MDA6 did not modify SB-mediated down-regulation of E2F-1 or c-Myc, but was associated with enhanced down-regulation of cyclins D1 and E. Together, these findings indicate that in U937 leukemia cells, p21WAF1/CIP1/MDA6 plays a critical functional role in SB-mediated G1 arrest and maturation, and suggest that cells displaying dysregulation of this CDKI respond to SB by engaging a default apoptotic program.

3/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11160763 21214429 PMID: 11313967
Downregulation of MLL-CBP fusion gene expression is associated with differentiation of SN-1 cells with t(11;16)(q23;p13).
Niitsu N; Hayashi Y; Honma Y
Saitama Cancer Center Research Institute, Ina-machi, Saitama 362-0806, Japan.
Oncogene (England) Jan 18 2001, 20 (3) p375-84, ISSN 0950-9232
Journal Code: 8711562
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The translocation t(11;16)(q23;p13) has only been documented in patients with acute leukemia or myelodysplasia secondary to therapy with drugs targeting DNA topoisomerase II. We have established a myeloid cell line (SN-1) with the MLL-CBP fusion gene from an acute leukemia patient with t(11;16)(q23;p13). Although SN-1 cells were not induced to differentiate by all-trans retinoic acid (ATRA) and 1alpha,25-dihydroxyvitamin D(3) (VD3), retinoid X receptor (RXR) agonists, such as 9-cis retinoic acid and Ro48-2250, effectively induced differentiation of the cells. Downregulation of the expression of the MLL-CBP fusion gene occurred during the differentiation of SN-1 cells. When SN-1 cells were treated with MLL-CBP **antisense** oligonucleotide, the cells were induced to differentiate by ATRA or VD3, suggesting that the MLL-CBP fusion gene dominant-negatively suppresses ATRA- or VD3-induced differentiation. Moreover, suboptimal concentrations of sodium butyrate, a **histone deacetylase** inhibitor, had a cooperative effect with ATRA or VD3 in inducing the differentiation of SN-1 cells. The downregulation of the expression of MLL-CBP mRNA was accompanied by the induction of differentiation. These findings suggest that RXR agonists or a clinically applicable combination of ATRA and butyrate derivatives might be useful for differentiation therapy in leukemia patients with the MLL-CBP fusion gene.

3/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11061211 21065182 PMID: 11134508
Blocking **histone** deacetylation in Arabidopsis induces pleiotropic effects on plant gene regulation and development.
Tian L; Chen Z J
Genetics Program and Department of Soil and Crop Sciences, Texas A&M University, College Station, TX 77843-2474, USA.
Proceedings of the National Academy of Sciences of the United States of America (United States) Jan 2 2001, 98 (1) p200-5, ISSN 0027-8424
Journal Code: 7505876
Contract/Grant No.: GM19072; GM; NIGMS

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Histone acetylation and deacetylation play essential roles in eukaryotic gene regulation. Reversible modifications of core histones are catalyzed by two intrinsic enzymes, **histone** acetyltransferase and **histone deacetylase** (HD). In general, **histone** deacetylation is related to transcriptional gene silencing, whereas acetylation correlates with gene activation. We produced transgenic plants expressing the **antisense** Arabidopsis HD (AtHD1) gene. AtHD1 is a homolog of human HD1 and RPD3 global transcriptional regulator in yeast. Expression of the **antisense** AtHD1 caused dramatic reduction in endogenous AtHD1 transcription, resulting in accumulation of acetylated histones, notably tetraacetylated H4. Reduction in AtHD1 expression and AtHD1 production and changes in acetylation profiles were associated with various developmental abnormalities, including early senescence, ectopic expression of silenced genes, suppression of apical dominance, homeotic changes, heterochronic shift toward juvenility, flower defects, and male and female sterility. Some of the phenotypes could be attributed to ectopic expression of tissue-specific genes (e.g., SUPERMAN) in vegetative tissues. No changes in genomic DNA methylation were detected in the transgenic plants. These results suggest that AtHD1 is a global regulator, which controls gene expression during development through DNA-sequence independent or epigenetic mechanisms in plants. In addition to DNA methylation, **histone** modifications may be involved in a general regulatory mechanism responsible for plant plasticity and variation in nature.

3/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11051109 21039633 PMID: 11196471
Mechanisms of epigenetic silencing of the c21 gene in Y1 adrenocortical tumor cells.
Szyf M; Slack A D
Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada. mszyf@pharma.mcgill.ca
Endocrine research (United States) Nov 2000, 26 (4) p921-30, ISSN 0743-5800 Journal Code: 8408548
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We utilized Y1 adrenocortical carcinoma cell line as a model system to dissect the events regulating epigenomic gene silencing in tumor cells. We show here that the chromatin structure of c21 gene is inactive in Y1 cells and that it could be reconfigured to an active form by either expressing **antisense** mRNA to DNA methyltransferase 1 (dnmt1) or an attenuator of Ras protooncogenic signaling hGAP. Surprisingly however, the known inducer of active chromatin structure the **histone deacetylase** inhibitor trichostatin A TSA fails to induce expression of c21. These results suggest that the primary cause of c21 gene silencing is independent of **histone** deacetylation. We present a model to explain the possible roles of the different components of the epigenome and the DNA methylation and demethylation machineries in silencing c21 gene expression.

3/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11012711 21003322 PMID: 11117260
Functional analysis of a RPD3 **histone deacetylase** homologue

in Arabidopsis thaliana.
Wu K; Malik K; Tian L; Brown D; Miki B
Eastern Cereal and Oilseed Research Centre, Agriculture and Agri-Food Canada, Ottawa, Ontario.
Plant molecular biology (Netherlands) Sep 2000, 44 (2) p167-76, ISSN 0167-4412 Journal Code: 9106343
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Histone acetylation is modulated through the action of **histone** acetyltransferase and **deacetylase**, which play key roles in the regulation of eukaryotic gene expression. We have screened the expressed sequence tag database with the yeast **histone deacetylase** RPD3 sequence and identified two Arabidopsis homologues, AtRPD3A and AtRPD3B. The deduced amino acid sequences of AtRPD3A and AtRPD3B show high overall homology (55% identity) to each other. AtRPD3A encodes a putative protein of 502 amino acids with 49% identity to the yeast RPD3. AtRPD3B encodes a putative protein of 471 amino acids and shares 55% amino acid identity with the yeast RPD3. Northern analysis indicated that AtRPD3A was highly expressed in the leaves, stems, flowers and young siliques of Arabidopsis plants, whereas the AtRPD3B transcript was not detected in these organs. An AtRPD3A fusion protein repressed transcription when directed to a promoter driving a reporter gene, indicating a role for AtRPD3A protein in gene repression. Arabidopsis plants were transformed with a gene construct comprising a truncated AtRPD3A cDNA in the **antisense** orientation driven by a strong constitutive promoter, -394tCUP. **Antisense** expression of AtRPD3A resulted in decreased endogenous AtRPD3A transcript and delayed flowering in transgenic Arabidopsis plants, suggesting that the transition from the vegetative to reproductive phase of development could be affected by **histone** acetylation. Our study demonstrates the important role of **histone** deacetylases in plant growth and development.

3/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10995279 20575461 PMID: 11135429
Keratin 23 (K23), a novel acidic keratin, is highly induced by **histone deacetylase** inhibitors during differentiation of pancreatic cancer cells.
Zhang J S; Wang L; Huang H; Nelson M; Smith D I
Division of Experimental Pathology, Department of Laboratory Medicine and Pathology, Mayo Foundation, Rochester, Minnesota 55905, USA.
Genes, chromosomes & cancer (UNITED STATES) Feb 2001, 30 (2) p123-35 , ISSN 1045-2257 Journal Code: 9007329
Contract/Grant No.: CA48031; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Sodium butyrate (NaBu) was shown to induce differentiation and apoptosis in the human pancreatic cancer cell line AsPC-1. A suppression subtractive hybridization-based technique was used to identify genes induced by NaBu. A novel cDNA was found to be highly up-regulated in AsPC-1 cells in response to NaBu. The gene expresses a 1.65-kb mRNA encoding a protein with an open reading frame of 422 amino acids. It has an intermediate filament signature sequence and extensive homology to type I keratins. Sequence comparison with known keratins indicated that the gene shares 42-46% amino acid identity and 60-65% similarity within the alpha-helical rod domain. The gene is named K23 (for human type I Keratin 23, KRT23). K23 mRNA was highly induced by NaBu in different pancreatic cancer cells. Trichostatin A (TSA), a potent and specific inhibitor of **histone deacetylase** ,

similarly induced K23 mRNA expression. Treatment with either actinomycin D or cycloheximide efficiently blocked the induction of K23 mRNA by NaBu/TSA. These results indicate that K23 mRNA induction by NaBu or TSA is a downstream event of **histone** hyperacetylation. We also demonstrated that expression of p21(WAF1/CIP1) **antisense** RNA efficiently blocked the induction of K23 mRNA induced by NaBu. Our results suggest that K23 is a novel member of the acidic keratin family that is induced in pancreatic cancer cells undergoing differentiation by a mechanism involving **histone** hyperacetylation. p21(WAF1/CIP1) serves as an important mediator during the induction process of K23 by NaBu. Copyright 2000 Wiley-Liss, Inc.

3/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10982029 20557638 PMID: 11108251
Allele-specific **histone** acetylation accompanies genomic imprinting of the insulin-like growth factor II receptor gene.
Hu J F; Pham J; Dey I; Li T; Vu T H; Hoffman A R
VA Palo Alto Health Care System, and Department of Medicine, Stanford University, California 94304, USA.
Endocrinology (UNITED STATES) Dec 2000, 141 (12) p4428-35, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: DK-36054; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The mouse insulin-like growth factor II receptor (Igf2r) gene encodes two reciprocally imprinted RNA transcripts: paternally imprinted Igf2r sense and maternally imprinted Igf2r **antisense**. Although DNA methylation has been implicated in the initiation and maintenance of genomic imprinting, acetylation of core histones has recently been appreciated as another important factor that regulates gene expression. To determine whether **histone** acetylation participates in the regulation of Igf2r imprinting, we examined the relative abundance of acetylated histones in interspecific mice (M. spretus x C57BL/6). Oligonucleosomes derived from liver were immunoprecipitated with acetyl-**histone** antiserum and were analyzed for the allelic distribution of DNA from the region of the sense and **antisense** Igf2r promoters. In nucleosomes associated with the Igf2r sense promoter, **histone** acetylation was demonstrated on the maternal allele, which is transcriptionally active. There was much less **histone** acetylation on the suppressed paternal allele. In nucleosomes associated with the Igf2r **antisense** promoter, the active paternal allele was heavily acetylated, whereas the suppressed maternal allele was underacetylated. Treatment of cultured fibroblasts with the **histone deacetylase** inhibitor Trichostatin A induces partial relaxation of genomic imprinting as well as decreased DNA methylation of both Igf2r sense and **antisense** promoters. These results demonstrate that increases in **histone** acetylation can lead to decreased DNA methylation, thereby modulating the regulation of the imprinted expression of Igf2r sense and **antisense** transcripts.

3/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10725936 20252855 PMID: 10792817
Functional analysis of HD2 **histone deacetylase** homologues in Arabidopsis thaliana.
Wu K; Tian L; Malik K; Brown D; Miki B
Eastern Cereal and Oilseed Research Centre, Agriculture and Agri-Food Canada, Ottawa, Ontario, Canada K1A 0C6.

Plant journal : for cell and molecular biology (ENGLAND) Apr 2000, 22 (1) p19-27, ISSN 0960-7412 Journal Code: 9207397
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Post-translational modification of histones, in particular acetylation, is an important mechanism in the regulation of eukaryotic gene expression. **Histone** deacetylases are enzymes that remove acetyl groups from the core histones and play a key role in the repression of transcription. HD2 is a maize **histone deacetylase**, which shows no sequence homology to the **histone** deacetylases identified from other eukaryotes. We have identified two putative HD2-like **histone deacetylase** cDNA clones, AtHD2A and AtHD2B, from Arabidopsis thaliana by screening the expressed sequence tag database. AtHD2A and AtHD2B encode putative proteins of 246 and 305 amino acids, and share 44% and 46% amino acid identity to the maize HD2, respectively. Northern blot analysis indicated that AtHD2A was highly expressed in flowers and young siliques of Arabidopsis plants, whereas AtHD2B was widely expressed in stems, leaves, flowers and young siliques. AtHD2A repressed transcription when directed to a promoter containing GAL4-binding sites as a GAL4 fusion protein. Deletion of the extended acidic domain or the domain containing predicted catalytic residues of AtHD2A resulted in the loss of gene repression activity, revealing the importance of both domains to AtHD2A function. Arabidopsis plants were transformed with a gene construct comprising an AtHD2A cDNA in the **antisense** orientation driven by a strong constitutive promoter, -394tCUP. Silencing of AtHD2A expression resulted in aborted seed development in transgenic Arabidopsis plants, suggesting that the AtHD2A gene product was important in the reproductive development of Arabidopsis thaliana.

3/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10635752 20180069 PMID: 10713164

SKIP, a CBF1-associated protein, interacts with the ankyrin repeat domain of NotchIC To facilitate NotchIC function.

Zhou S; Fujimuro M; Hsieh J J; Chen L; Miyamoto A; Weinmaster G; Hayward S D

Department of Pharmacology and Molecular Sciences, Johns Hopkins School of Medicine, Baltimore, Maryland 21205, USA.

Molecular and cellular biology (UNITED STATES) Apr 2000, 20 (7) p2400-10, ISSN 0270-7306 Journal Code: 8109087
Contract/Grant No.: RO1 CA42245; CA; NCI; RO1 NS31885; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Notch proteins are transmembrane receptors that mediate intercell communication and direct individual cell fate decisions. The activated intracellular form of Notch, NotchIC, translocates to the nucleus, where it targets the DNA binding protein CBF1. CBF1 mediates transcriptional repression through the recruitment of an SMRT-**histone deacetylase**-containing corepressor complex. We have examined the mechanism whereby NotchIC overcomes CBF1-mediated transcriptional repression. We identified SKIP (Ski-interacting protein) as a CBF1 binding protein in a yeast two-hybrid screen. Both CBF1 and SKIP are highly conserved evolutionarily, and the SKIP-CBF1 interaction is also conserved in assays using the Caenorhabditis elegans and Drosophila melanogaster SKIP homologs. Protein-protein interaction assays demonstrated interaction between SKIP and the corepressor SMRT. More surprisingly, SKIP also interacted with NotchIC. The SMRT and NotchIC interactions were mutually exclusive. In competition binding experiments SMRT displaced NotchIC from

CBF1 and from SKIP. Contact with SKIP is required for biological activity of NotchIC. A mutation in the fourth ankyrin repeat that abolished Notch signal transduction did not affect interaction with CBF1 but abolished interaction with SKIP. Further, NotchIC was unable to block muscle cell differentiation in myoblasts expressing **antisense** SKIP. The results suggest a model in which NotchIC activates responsive promoters by competing with the SMRT-corepressor complex for contacts on both CBF1 and SKIP.

3/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10312424 99310537 PMID: 10383164

Carboxypeptidase A3 (CPA3): a novel gene highly induced by **histone deacetylase** inhibitors during differentiation of prostate epithelial cancer cells.

Huang H; Reed C P; Zhang J S; Shridhar V; Wang L; Smith D I
Department of Laboratory Medicine and Pathology, Mayo Foundation, Rochester, Minnesota 55905, USA.

Cancer research (UNITED STATES) Jun 15 1999, 59 (12) p2981-8, ISSN 0008-5472 Journal Code: 2984705R
Contract/Grant No.: CA48031; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Butyrate and its structural analogues have recently entered clinical trials as a potential drug for differentiation therapy of advanced prostate cancer. To better understand the molecular mechanism(s) involved in prostate cancer differentiation, we used mRNA differential display to identify the gene(s) induced by butyrate. We found that the androgen-independent prostate cancer cell line PC-3 undergoes terminal differentiation and apoptosis after treatment with sodium butyrate (NaBu). A novel cDNA designated carboxypeptidase A3 (CPA3), which was up-regulated in NaBu-treated PC-3 cells, was identified and characterized. This gene expresses a 2795-bp mRNA encoding a protein with an open reading frame of 421 amino acids. CPA3 has 37-63% amino acid identity with zinc CPs from different mammalian species. It also shares 27-43% amino acid similarity with zinc CPs from several nonmammalian species, including Escherichia coli, yeast, Caenorhabditis elegans, and Drosophila. The structural similarity between CPA3 and its closest homologues indicates that the putative CPA3 protein contains a 16-residue signal peptide sequence, a 95-residue NH2-terminal activation segment, and a 310-residue CP enzyme domain. The consistent induction of CPA3 by NaBu in several prostate cancer cell lines led us to investigate the signaling pathway involved in the induction of CPA3 mRNA. Trichostatin A, a potent and specific inhibitor of **histone deacetylase**, also induced CPA3 mRNA expression, suggesting that CPA3 gene induction is mediated by **histone** hyperacetylation. We demonstrated that CPA3 induction was a downstream effect of the treatment with butyrate or trichostatin A, but that the induction of p21(WAF1/CIP1) occurred immediately after these treatments. We also demonstrated that the induction of CPA3 mRNA by NaBu was inhibited by p21(WAF1/CIP1) **antisense** mRNA expression, indicating that p21 transactivation is required for the induction of CPA3 by NaBu. Our data demonstrate that the **histone** hyperacetylation signaling pathway is activated during NaBu-mediated differentiation of PC-3 cells, and the new gene, CPA3, is involved in this pathway.

3/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10268735 99253746 PMID: 10321829

Both Sp1 and Sp3 are responsible for p21waf1 promoter activity induced by **histone deacetylase** inhibitor in NIH3T3 cells.

Xiao H; Hasegawa T; Isobe K
Department of Basic Gerontology, National Institute for Longevity Sciences, Aichi, Japan.

Journal of cellular biochemistry (UNITED STATES) Jun 1 1999, 73 (3) p291-302, ISSN 0730-2312 Journal Code: 8205768
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Histone deacetylase inhibitor-induced expression of p21WAF1 is p53 independent. In the present study, we provide evidence that trichostatin A (TSA), a specific inhibitor of **histone deacetylase**, can elevate H3 and H4 acetylation and p21WAF1 expression in NIH3T3 cells at first. To identify the transcription factor which is responsible for **histone deacetylase** inhibitor-induced expression of p21WAF1 and understand the potential events occurred during this process, we analyze the response of the mouse p21WAF1 promoter to TSA in detail. The region responsive to TSA treatment in the p21 promoter is located -100 bp upstream from transcription initiation site and contains a GC-box. The mutation introduced into this GC-box decreases most of the basal and TSA-induced promoter activity. The results from gel-shift assay show that Sp1 and Sp3 bind to this GC-rich region. Cotransfection with Sp1 and/or Sp3 expression constructs elevate both basal and induced promoter activity, and this elevation is dependent on the present of the GC-box. By contrast, cotransfection with reverse oriented Sp1 or Sp3 cDNA decreased basal and induced-promoter activity, as well as GC-box dependency. These findings provide physical and functional evidence which strongly indicated that both Sp1 and Sp3 are responsible for TSA-induced transactivation of the murine p21WAF1 promoter in NIH3T3 cells.

3/3,AB/14 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13543768 BIOSIS NO.: 200200172589
PATZ attenuates the RNF4-mediated enhancement of androgen receptor-dependent transcription.

AUTHOR: Pero Raffaela; Lembo Francesca; Palmieri Emiliano Antonio; Vitiello Carmen; Fedele Monica; Fusco Alfredo; Bruni Carmelo Bruno; Chiariotti Lorenzo(a)
AUTHOR ADDRESS: (a)Dipartimento di Medicina Sperimentale e Clinica "G. Salvatore", Universita degli Studi di Catanzaro "Magna Graecia", Via Tommaso Campanella 115, 88100, Catanzaro**Italy E-Mail: chiariot@unina.it

JOURNAL: Journal of Biological Chemistry 277 (5):p3280-3285 February, 2002
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PATZ is a transcriptional repressor affecting the basal activity of different promoters, whereas RNF4 is a transcriptional activator. The association of PATZ with RNF4 switches the activation to repression of selected basal promoters. Because RNF4 interacts also with the androgen receptor (AR) functioning as a coactivator and, in turn, RNF4 associates with PATZ, we investigated whether PATZ functions as an AR coregulator. We demonstrate that PATZ does not influence directly the AR response but acts as an AR corepressor in the presence of RNF4. Such repression is not dependent on **histone** deacetylases. A mutant RNF4 that does not bind PATZ but enhances AR-dependent transcription is not influenced by PATZ, demonstrating that the repression by PATZ occurs only upon binding to

RNF4. We also demonstrate that RNF4, AR, and PATZ belong to the same complex in vivo also in the presence of androgen, suggesting that repression is not mediated by the displacement of RNF4 from AR. Finally, we show that the repression of endogenous PATZ expression by **antisense** expression plasmids in LNCaP cells results in a stronger androgen response. Our findings demonstrate that PATZ is a novel AR coregulator that acts by modulating the effect of a coactivator. This could represent a novel and more general mechanism to finely tune the androgen response.

2002

3/3,AB/15 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13306009 BIOSIS NO.: 200100513158
Maize **histone** deacetylases and their use.
AUTHOR: Baldwin Donald Adelphi(a); Briggs Steven P; Crane Virginia C
AUTHOR ADDRESS: (a)Des Moines, IA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1250 (2):pNo Pagination Sep. 11, 2001
MEDIUM: e-file
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Histone** deacetylases and nucleotide sequences encoding said **histone** deacetylases are provided. The sequences as well as corresponding **antisense** constructs are useful for modulating gene activity in plants. Additionally, the sequences are useful for enhancing disease resistance in transformed plants.

2001

3/3,AB/16 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13273896 BIOSIS NO.: 200100481045
Antisense histone deacetylase 1 expression increases apoptosis mediated by sodium butyrate in human melanoma cells.
AUTHOR: Medrano E(a); Bandyopadhyay D
AUTHOR ADDRESS: (a)Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX**USA
JOURNAL: Journal of Investigative Dermatology 117 (2):p484 August, 2001
MEDIUM: print
CONFERENCE/MEETING: 62nd Annual Meeting of the Society for Investigative Dermatology Washington, DC, USA May 09-12, 2001
ISSN: 0022-202X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

3/3,AB/17 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13184681 BIOSIS NO.: 200100391830

Antisense histone deacetylase 1 expression increases apoptosis mediated by sodium butyrate in human melanoma cells.
AUTHOR: Bandyopadhyay Debdutta(a); Medrano Estela E(a)
AUTHOR ADDRESS: (a)Baylor College of Medicine, Houston, TX**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42p132 March, 2001
MEDIUM: print
CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

3/3,AB/18 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13086625 BIOSIS NO.: 200100293774
Phase I trial of GenasenseTM (G3139, GENTA, INC.), a BCL-2 **antisense** (AS), in refractory (REF) or relapsed (REL) acute leukemia (AL).
AUTHOR: Marcucci G(a); Bloomfield C D(a); Balcerzak S P(a); Kourlas P J(a); Stanley H R(a); Fingert H; Maghraby E A(a); Lucas D(a); Chen K K(a); Byrd J C(a); Kraut E H(a); Grever M R(a); Caligiuri M A(a)
AUTHOR ADDRESS: (a)The Comprehensive Cancer Center, The Ohio State University, Columbus, OH**USA
JOURNAL: Blood 96 (11 Part 1):p119a November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In AL a strong association between chemotherapy resistance and overexpression of BCL-2 exists. We hypothesized that chemotherapy-induced apoptosis is enhanced by BCL-2 downregulation. G3139 is a BCL-2 AS that downregulates BCL-2 expression in vitro and in vivo. We report on 10 pts enrolled at levels 1-3 of a Phase I study with G3139 + fludarabine, ARA-C, and G-CSF (FLAG) therapy for REF/REL AL. G3139 (4mg/kg/day) is given on d1-10, whereas both fludarabine (starting @ 15mg/m2) and ARA-C (starting @ 1000 mg/m2) are given on d6-10 and escalated in successive cohorts. Therapy-related fever, nausea, emesis, hypocalcemia, hypophosphatemia, and fluid retention were not dose-limiting. Hematologic toxicities were as expected. Steady state G3139 plasma levels exceeding the relevant target level (1mug/ml) were achieved after 24h. Quantification of BCL-2 levels in AL blasts will be presented. Three pts achieved CR and received a 2nd course of therapy, two continue with NED at d53 and 111. Two pts had NED but persistent neutropenia/thrombocytopenia at d52 and 55; one of them continues with NED at d76. Three of 5 responders had prior **HDAC**. One patient had leukostasis at d6, and was taken off study. The data suggest that G3139 is feasible for addition to multicycle cycle induction regimens for AL; moreover the encouraging 50% response rate-including pts with REF AL and prior **HDAC** - supports further development of G3139 of G3139 in combination regimens for REL/REF AL.

2000
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              52  AU=LI Z K
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           96  AU=LI Z W
           73  AU=LI Z X
          143  AU=LI Z Y
           32  AU=LI Z Z
            1  AU=LI Z-A
            3  AU=LI Z-B
           29  AU=LI Z-C
            8  AU=LI Z-D
           17  AU=LI Z-F
           18  AU=LI Z-G
           69  AU=LI Z-H
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Set      Items   Description
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S5        4081   E3-E48
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? s s13 and hdac
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? s s13 and histon?
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E12         2  AU=BESTERS B

          Enter P or PAGE for more
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              2  AU=BESTERMAN JEFF
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Set      Items   Description
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S10         34   RD (unique items)
S11          0   S10 AND HISTON?
S12          0   S10 AND HDAC
S13         18   S5 AND ANTISENS?
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? s (s16 or s19)
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     S23        0  S22 AND ANTISEN?
? s s22 and hdac
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            707  HDAC
     S24        2  S22 AND HDAC
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 24/3,AB/1      (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13356110   22058272   PMID: 12061890
  Structurally simple trichostatin A-like straight chain hydroxamates as
potent histone deacetylase inhibitors.
  Woo Soon Hyung; Frechette Sylvie; Abou Khalil Elie; Bouchain Giliane;
Vaisburg Arkadii; Bernstein Naomy; Moradei Oscar; Leit Silvana; Allan
Martin; Fournel Marielle; Trachy-Bourget Marie-Claude; Li Zuomei;
Besterman Jeffrey M; Delorme Daniel
  Departments of Medicinal Chemistry and Molecular Biology, MethylGene
Inc., 7220 Frederick-Banting, Montreal, Quebec H4S 2A1, Canada.
  Journal of medicinal chemistry (United States)  Jun 20 2002,  45  (13)
 p2877-85,  ISSN 0022-2623   Journal Code: 9716531
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  A series of new, structurally simple trichostatin A (TSA)-like straight
chain hydroxamates were prepared and evaluated for their ability to inhibit
partially purified human histone deacetylase 1 (HDAC-1). Some
of these compounds such as 8m, 8n, 12, and 15b exhibited potent HDAC
inhibitory activity with low nanomolar IC(50) values, comparable to natural
TSA. These compounds induce hyperacetylation of histones in T24 human
cancer cells and significantly inhibit proliferation in various human
cancer cells. They also induce expression of p21 and cause cell cycle
blocks in human cancer cells. In this paper, we describe the synthesis of
these new compounds as well as structure-activity relationship results from
enzyme inhibition and alterations in cellular function.


 24/3,AB/2      (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13327769   BIOSIS NO.: 200100534918
Design and synthesis of a novel class of histone deacetylase
  inhibitors.
AUTHOR: Lavoie Rico; Bouchain Giliane; Frechette Sylvie; Woo Soon Hyung;
  Khalil Elie Abou; Leit Silvana; Fournel Marielle; Yan Pu T;
  Trachy-Bourget Marie-Claude; Beaulieu Carole; Li Zuomei; Besterman
  Jeffrey; Delorme Daniel(a
AUTHOR ADDRESS: (a)Department of Medicinal Chemistry, MethylGene Inc., 7220
  Frederick-Banting, Montreal, Quebec, H4S 2A1: delormed@methylgene.com**
  Canada
JOURNAL: Bioorganic & Medicinal Chemistry Letters  11 (21):p2847-2850 5
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November, 2001
MEDIUM: print
ISSN: 0960-894X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Histone** deacetylase inhibitors (HDACs) have emerged as a novel class of antiproliferative agents. Utilizing structure-based design, the synthesis of a series of sulfonamide hydroxamic acids is described. Further optimization of this series by substitution of the terminal aromatic ring yielded **HDAC** inhibitors with good in vitro and in vivo activities.

2001
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 e au=bonfils, claire

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S21            3   S20 AND HISTON?
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S24            2   S22 AND HDAC
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S26           84   E3-E5
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                84  S26
     S27        84  S25 OR S26
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 30/3,AB/1      (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10669497   20219106   PMID: 10753866
  Characterization of the human DNA methyltransferase splice variant
Dnmt1b.
  Bonfils C; Beaulieu N; Chan E; Cotton-Montpetit J; MacLeod A R
  MethylGene Inc., Montreal, Quebec H4S 2A1, Canada.
  Journal of biological chemistry (UNITED STATES)  Apr 14 2000,  275  (15)
  p10754-60,  ISSN 0021-9258  Journal Code: 2985121R
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Tissue- and gene-specific patterns of cytosine-DNA methylation are
characteristic features of vertebrate genomes. The generation and proper
maintenance of DNA methylation patterns are essential for embryonic
development, as demonstrated by the lethal phenotypes of mice with either a
targeted disruption of Dnmt1, the gene responsible for the maintenance of
DNA methylation, or targeted disruption of Dnmt3a or Dnmt3b, the genes
involved in generation of newly formed methylation patterns. Recently, a
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novel mRNA, Dnmt1b, resulting from alternative splicing of Dnmt1 was identified (Hsu, D. W., Lin, M. J., Lee, T. L., Wen, S. C., Chen, X., and Shen, C. K., (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 9751-9756). The abundance of Dnmt1b mRNA was estimated by semiquantitative reverse transcription polymerase chain reaction and was suggested to encode a major C-5 DNA methyltransferase isoform. Here we report characterization of this novel DNA methyltransferase transcript, Dnmt1b, and its protein product in human cell lines and in freshly isolated human peripheral blood mononuclear cells. The abundance of Dnmt1b transcript, as determined by quantitative RNase protection analysis, was determined to range from 6% to 25% of Dnmt1 in human cells. Second generation **antisense** inhibitors targeted to the 5'- and 3'-ends of Dnmt1 inhibited the accumulation of both Dnmt1 and Dnmt1b in cells. Dnmt1b protein purified from a baculovirus expression system was demonstrated to be a functional DNA methyltransferase, and to have Michaelis constants for both DNA and S-adenosyl-L-methionine similar to baculovirus-expressed Dnmt1. However, antibodies raised against Dnmt1b epitopes demonstrated that Dnmt1b protein was present at approximately 2-5% of the level of Dnmt1 and therefore represents only a minor DNA methyltransferase isoform in human cells.
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d deacetylase
           36219  HISTONE
            3795  DEACETYLASE
     S31    2943  HISTONE AND DEACETYLASE
? s s31 and antisens?
            2943  S31
           34724  ANTISENS?
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Processing
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 34/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11051109   21039633   PMID: 11196471
  Mechanisms of epigenetic silencing of the c21 gene in Y1 adrenocortical
tumor cells.
  Szyf M; Slack A D
  Department of Pharmacology and Therapeutics, McGill University, Montreal,
Quebec, Canada. mszyf@pharma.mcgill.ca
  Endocrine research (United States)  Nov 2000,  26  (4)  p921-30,
ISSN 0743-5800   Journal Code: 8408548
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  We utilized Y1 adrenocortical carcinoma cell line as a model system to
dissect the events regulating epigenomic gene silencing in tumor cells. We
show here that the chromatin structure of c21 gene is inactive in Y1 cells
and that it could be reconfigured to an active form by either expressing
antisense mRNA to DNA methyltransferase 1 (dnmt1) or an attenuator of
Ras protooncogenic signaling hGAP. Surprisingly however, the known inducer
of active chromatin structure the histone deacetylase inhibitor
trichostatin A TSA fails to induce expression of c21. These results suggest
that the primary cause of c21 gene silencing is independent of
histone deacetylation. We present a model to explain the possible
roles of the different components of the epigenome and the DNA methylation
and demethylation machineries in silencing c21 gene expression.


 34/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11012711   21003322   PMID: 11117260
   Functional analysis of a RPD3 histone deacetylase homologue
in Arabidopsis thaliana.
  Wu K; Malik K; Tian L; Brown D; Miki B
  Eastern Cereal and Oilseed Research Centre, Agriculture and Agri-Food
Canada, Ottawa, Ontario.
  Plant molecular biology (Netherlands)  Sep 2000,  44  (2)  p167-76
,  ISSN 0167-4412   Journal Code: 9106343
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Histone acetylation is modulated through the action of
histone acetyltransferase and deacetylase, which play key roles
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in the regulation of eukaryotic gene expression. We have screened the expressed sequence tag database with the yeast **histone deacetylase** RPD3 sequence and identified two Arabidopsis homologues, AtRPD3A and AtRPD3B. The deduced amino acid sequences of AtRPD3A and AtRPD3B show high overall homology (55% identity) to each other. AtRPD3A encodes a putative protein of 502 amino acids with 49% identity to the yeast RPD3. AtRPD3B encodes a putative protein of 471 amino acids and shares 55% amino acid identity with the yeast RPD3. Northern analysis indicated that AtRPD3A was highly expressed in the leaves, stems, flowers and young siliques of Arabidopsis plants, whereas the AtRPD3B transcript was not detected in these organs. An AtRPD3A fusion protein repressed transcription when directed to a promoter driving a reporter gene, indicating a role for AtRPD3A protein in gene repression. Arabidopsis plants were transformed with a gene construct comprising a truncated AtRPD3A cDNA in the **antisense** orientation driven by a strong constitutive promoter, -394tCUP. **Antisense** expression of AtRPD3A resulted in decreased endogenous AtRPD3A transcript and delayed flowering in transgenic Arabidopsis plants, suggesting that the transition from the vegetative to reproductive phase of development could be affected by **histone** acetylation. Our study demonstrates the important role of **histone** deacetylases in plant growth and development.

34/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10982029 20557638 PMID: 11108251

Allele-specific **histone** acetylation accompanies genomic imprinting of the insulin-like growth factor II receptor gene.

Hu J F; Pham J; Dey I; Li T; Vu T H; Hoffman A R

VA Palo Alto Health Care System, and Department of Medicine, Stanford University, California 94304, USA.

Endocrinology (UNITED STATES) Dec **2000**, 141 (12) p4428-35, ISSN 0013-7227 Journal Code: 0375040

Contract/Grant No.: DK-36054; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The mouse insulin-like growth factor II receptor (Igf2r) gene encodes two reciprocally imprinted RNA transcripts: paternally imprinted Igf2r sense and maternally imprinted Igf2r **antisense**. Although DNA methylation has been implicated in the initiation and maintenance of genomic imprinting, acetylation of core histones has recently been appreciated as another important factor that regulates gene expression. To determine whether **histone** acetylation participates in the regulation of Igf2r imprinting, we examined the relative abundance of acetylated histones in interspecific mice (M. spretus x C57BL/6). Oligonucleosomes derived from liver were immunoprecipitated with acetyl-**histone** antiserum and were analyzed for the allelic distribution of DNA from the region of the sense and **antisense** Igf2r promoters. In nucleosomes associated with the Igf2r sense promoter, **histone** acetylation was demonstrated on the maternal allele, which is transcriptionally active. There was much less **histone** acetylation on the suppressed paternal allele. In nucleosomes associated with the Igf2r **antisense** promoter, the active paternal allele was heavily acetylated, whereas the suppressed maternal allele was underacetylated. Treatment of cultured fibroblasts with the **histone deacetylase** inhibitor Trichostatin A induces partial relaxation of genomic imprinting as well as decreased DNA methylation of both Igf2r sense and **antisense** promoters. These results demonstrate that increases in **histone** acetylation can lead to decreased DNA methylation, thereby modulating the regulation of the imprinted expression of Igf2r sense and **antisense** transcripts.

34/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10725936 20252855 PMID: 10792817
Functional analysis of HD2 **histone deacetylase** homologues in Arabidopsis thaliana.
Wu K; Tian L; Malik K; Brown D; Miki B
Eastern Cereal and Oilseed Research Centre, Agriculture and Agri-Food Canada, Ottawa, Ontario, Canada K1A 0C6.
Plant journal : for cell and molecular biology (ENGLAND) Apr **2000**, 22 (1) p19-27, ISSN 0960-7412 Journal Code: 9207397
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Post-translational modification of histones, in particular acetylation, is an important mechanism in the regulation of eukaryotic gene expression. **Histone** deacetylases are enzymes that remove acetyl groups from the core histones and play a key role in the repression of transcription. HD2 is a maize **histone deacetylase**, which shows no sequence homology to the **histone** deacetylases identified from other eukaryotes. We have identified two putative HD2-like **histone deacetylase** cDNA clones, AtHD2A and AtHD2B, from Arabidopsis thaliana by screening the expressed sequence tag database. AtHD2A and AtHD2B encode putative proteins of 246 and 305 amino acids, and share 44% and 46% amino acid identity to the maize HD2, respectively. Northern blot analysis indicated that AtHD2A was highly expressed in flowers and young siliques of Arabidopsis plants, whereas AtHD2B was widely expressed in stems, leaves, flowers and young siliques. AtHD2A repressed transcription when directed to a promoter containing GAL4-binding sites as a GAL4 fusion protein. Deletion of the extended acidic domain or the domain containing predicted catalytic residues of AtHD2A resulted in the loss of gene repression activity, revealing the importance of both domains to AtHD2A function. Arabidopsis plants were transformed with a gene construct comprising an AtHD2A cDNA in the **antisense** orientation driven by a strong constitutive promoter, -394tCUP. Silencing of AtHD2A expression resulted in aborted seed development in transgenic Arabidopsis plants, suggesting that the AtHD2A gene product was important in the reproductive development of Arabidopsis thaliana.

34/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10635752 20180069 PMID: 10713164
SKIP, a CBF1-associated protein, interacts with the ankyrin repeat domain of NotchIC To facilitate NotchIC function.
Zhou S; Fujimuro M; Hsieh J J; Chen L; Miyamoto A; Weinmaster G; Hayward S D
Department of Pharmacology and Molecular Sciences, Johns Hopkins School of Medicine, Baltimore, Maryland 21205, USA.
Molecular and cellular biology (UNITED STATES) Apr **2000**, 20 (7) p2400-10, ISSN 0270-7306 Journal Code: 8109087
Contract/Grant No.: RO1 CA42245; CA; NCI; RO1 NS31885; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Notch proteins are transmembrane receptors that mediate intercell communication and direct individual cell fate decisions. The activated intracellular form of Notch, NotchIC, translocates to the nucleus, where it targets the DNA binding protein CBF1. CBF1 mediates transcriptional repression through the recruitment of an SMRT-**histone**

deacetylase -containing corepressor complex. We have examined the mechanism whereby NotchIC overcomes CBF1-mediated transcriptional repression. We identified SKIP (Ski-interacting protein) as a CBF1 binding protein in a yeast two-hybrid screen. Both CBF1 and SKIP are highly conserved evolutionarily, and the SKIP-CBF1 interaction is also conserved in assays using the Caenorhabditis elegans and Drosophila melanogaster SKIP homologs. Protein-protein interaction assays demonstrated interaction between SKIP and the corepressor SMRT. More surprisingly, SKIP also interacted with NotchIC. The SMRT and NotchIC interactions were mutually exclusive. In competition binding experiments SMRT displaced NotchIC from CBF1 and from SKIP. Contact with SKIP is required for biological activity of NotchIC. A mutation in the fourth ankyrin repeat that abolished Notch signal transduction did not affect interaction with CBF1 but abolished interaction with SKIP. Further, NotchIC was unable to block muscle cell differentiation in myoblasts expressing **antisense** SKIP. The results suggest a model in which NotchIC activates responsive promoters by competing with the SMRT-corepressor complex for contacts on both CBF1 and SKIP.

34/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10312424 99310537 PMID: 10383164

Carboxypeptidase A3 (CPA3): a novel gene highly induced by **histone deacetylase** inhibitors during differentiation of prostate epithelial cancer cells.

Huang H; Reed C P; Zhang J S; Shridhar V; Wang L; Smith D I
Department of Laboratory Medicine and Pathology, Mayo Foundation, Rochester, Minnesota 55905, USA.

Cancer research (UNITED STATES) Jun 15 **1999**, 59 (12) p2981-8, ISSN 0008-5472 Journal Code: 2984705R
Contract/Grant No.: CA48031; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Butyrate and its structural analogues have recently entered clinical trials as a potential drug for differentiation therapy of advanced prostate cancer. To better understand the molecular mechanism(s) involved in prostate cancer differentiation, we used mRNA differential display to identify the gene(s) induced by butyrate. We found that the androgen-independent prostate cancer cell line PC-3 undergoes terminal differentiation and apoptosis after treatment with sodium butyrate (NaBu). A novel cDNA designated carboxypeptidase A3 (CPA3), which was up-regulated in NaBu-treated PC-3 cells, was identified and characterized. This gene expresses a 2795-bp mRNA encoding a protein with an open reading frame of 421 amino acids. CPA3 has 37-63% amino acid identity with zinc CPs from different mammalian species. It also shares 27-43% amino acid similarity with zinc CPs from several nonmammalian species, including Escherichia coli, yeast, Caenorhabditis elegans, and Drosophila. The structural similarity between CPA3 and its closest homologues indicates that the putative CPA3 protein contains a 16-residue signal peptide sequence, a 95-residue NH2-terminal activation segment, and a 310-residue CP enzyme domain. The consistent induction of CPA3 by NaBu in several prostate cancer cell lines led us to investigate the signaling pathway involved in the induction of CPA3 mRNA. Trichostatin A, a potent and specific inhibitor of **histone deacetylase** , also induced CPA3 mRNA expression, suggesting that CPA3 gene induction is mediated by **histone** hyperacetylation. We demonstrated that CPA3 induction was a downstream effect of the treatment with butyrate or trichostatin A, but that the induction of p21(WAF1/CIP1) occurred immediately after these treatments. We also demonstrated that the induction of CPA3 mRNA by NaBu was inhibited by p21(WAF1/CIP1) **antisense** mRNA expression, indicating that p21

transactivation is required for the induction of CPA3 by NaBu. Our data demonstrate that the **histone** hyperacetylation signaling pathway is activated during NaBu-mediated differentiation of PC-3 cells, and the new gene, CPA3, is involved in this pathway.

34/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10268735 99253746 PMID: 10321829
Both Sp1 and Sp3 are responsible for p21waf1 promoter activity induced by **histone deacetylase** inhibitor in NIH3T3 cells.
Xiao H; Hasegawa T; Isobe K
Department of Basic Gerontology, National Institute for Longevity Sciences, Aichi, Japan.
Journal of cellular biochemistry (UNITED STATES) Jun 1 **1999**, 73 (3) p291-302, ISSN 0730-2312 Journal Code: 8205768
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Histone deacetylase inhibitor-induced expression of p21WAF1 is p53 independent. In the present study, we provide evidence that trichostatin A (TSA), a specific inhibitor of **histone deacetylase**, can elevate H3 and H4 acetylation and p21WAF1 expression in NIH3T3 cells at first. To identify the transcription factor which is responsible for **histone deacetylase** inhibitor-induced expression of p21WAF1 and understand the potential events occurred during this process, we analyze the response of the mouse p21WAF1 promoter to TSA in detail. The region responsive to TSA treatment in the p21 promoter is located -100 bp upstream from transcription initiation site and contains a GC-box. The mutation introduced into this GC-box decreases most of the basal and TSA-induced promoter activity. The results from gel-shift assay show that Sp1 and Sp3 bind to this GC-rich region. Cotransfection with Sp1 and/or Sp3 expression constructs elevate both basal and induced promoter activity, and this elevation is dependent on the present of the GC-box. By contrast, cotransfection with reverse oriented Sp1 or Sp3 cDNA decreased basal and induced-promoter activity, as well as GC-box dependency. These findings provide physical and functional evidence which strongly indicated that both Sp1 and Sp3 are responsible for TSA-induced transactivation of the murine p21WAF1 promoter in NIH3T3 cells.

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 s hdac and antisens?
             707  HDAC
           34724  ANTISENS?
     S35       1  HDAC AND ANTISENS?
? t s35/3,ab/all

 35/3,AB/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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13086625   BIOSIS NO.: 200100293774
Phase I trial of GenasenseTM (G3139, GENTA, INC.), a BCL-2 antisense
  (AS), in refractory (REF) or relapsed (REL) acute leukemia (AL).
AUTHOR: Marcucci G(a); Bloomfield C D(a); Balcerzak S P(a); Kourlas P J(a);
  Stanley H R(a); Fingert H; Maghraby E A(a); Lucas D(a); Chen K K(a); Byrd
  J C(a); Kraut E H(a); Grever M R(a); Caligiuri M A(a)
AUTHOR ADDRESS: (a)The Comprehensive Cancer Center, The Ohio State
  University, Columbus, OH**USA
JOURNAL: Blood  96 (11 Part 1):p119a November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of
Hematology  San Francisco, California, USA  December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In AL a strong association between chemotherapy resistance and
  overexpression of BCL-2 exists. We hypothesized that chemotherapy-induced
  apoptosis is enhanced by BCL-2 downregulation. G3139 is a BCL-2 AS that
  downregulates BCL-2 expression in vitro and in vivo. We report on 10 pts
  enrolled at levels 1-3 of a Phase I study with G3139 + fludarabine,
  ARA-C, and G-CSF (FLAG) therapy for REF/REL AL. G3139 (4mg/kg/day) is
  given on d1-10, whereas both fludarabine (starting @ 15mg/m2) and ARA-C
  (starting @ 1000 mg/m2) are given on d6-10 and escalated in successive
  cohorts. Therapy-related fever, nausea, emesis, hypocalcemia,
  hypophosphatemia, and fluid retention were not dose-limiting. Hematologic
  toxicities were as expected. Steady state G3139 plasma levels exceeding
  the relevant target level (1mug/ml) were achieved after 24h.
  Quantification of BCL-2 levels in AL blasts will be presented. Three pts
  achieved CR and received a 2nd course of therapy, two continue with NED
  at d53 and 111. Two pts had NED but persistent
  neutropenia/thrombocytopenia at d52 and 55; one of them continues with
  NED at d76. Three of 5 responders had prior HDAC. One patient had
  leukostasis at d6, and was taken off study. The data suggest that G3139
  is feasible for addition to multicycle cycle induction regimens for AL;
  moreover the encouraging 50% response rate-including pts with REF AL and
  prior HDAC - supports further development of G3139 of G3139 in
  combination regimens for REL/REF AL.

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Dialog Word Search plus Inventor Searches

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? s hdac or (histone and deacetylase)
             707  HDAC
           36219  HISTONE
            3795  DEACETYLASE
      S1    3094  HDAC OR (HISTONE AND DEACETYLASE)
? s s1 and (antisens? or ribozym?)
            3094  S1
           34724  ANTISENS?
            6012  RIBOZYM?
      S2      30  S1 AND (ANTISENS? OR RIBOZYM?)
? rd
...completed examining records
      S3      18  RD (unique items)
? t s3/3,ab/all

 3/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13106953   21945948   PMID: 11948399
  Metastasis-associated protein (MTA)1 enhances migration, invasion, and
anchorage-independent survival of immortalized human keratinocytes.
  Mahoney My G; Simpson Anisha; Jost Monika; Noe Mariadele; Kari Csaba;
Pepe Deanna; Choi Yoo Won; Uitto Jouni; Rodeck Ulrich
  Department of Dermatology and Cutaneous Biology, Jefferson Medical
College, and Jefferson Institute of Molecular Medicine, Thomas Jefferson
University, Philadelphia, Pennsylvania, PA 19107, USA.
My.Mahoney@mail.tju.edu
  Oncogene (England) Mar 28 2002, 21 (14) p2161-70, ISSN 0950-9232
Journal Code: 8711562
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The human metastasis-associated gene (MTA1), a member of the nucleosome
remodeling complex with histone deacetylase activity, is
frequently overexpressed in biologically aggressive epithelial neoplasms.
Here, we extend this observation to squamous carcinoma cells, which express
high levels of MTA1 relative to normal or immortalized keratinocytes. To
address functional aspects of MTA1 expression, we established variants of
human immortalized keratinocytes (HaCaT cells) by expressing MTA1 cDNA in
both the sense and antisense orientations. We demonstrate that (1)
forced MTA1 expression enhances migration and invasion of immortalized
keratinocytes; (2) MTA1 expression is necessary but not sufficient for cell
survival in the anchorage independent state; (3) MTA1 contributes to
expression of the anti-apoptotic Bcl-2 family member Bcl-x(L); (4) MTA1
expression in immortalized keratinocytes depends, in part, on activation of
the epidermal growth factor receptor (EGFR). These results establish that,
in keratinocytes, MTA1 expression contributes to several aspects of the
metastatic phenotype including survival in the anchorage independent state,
migration, and invasion.


 3/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11297218   21336585   PMID: 11337508
  Sodium butyrate induces transcription from the G alpha(i2) gene promoter
through multiple Sp1 sites in the promoter and by activating the MEK-ERK
signal transduction pathway.
  Yang J; Kawai Y; Hanson R W; Arinze I J
  Department of Biochemistry, Meharry Medical College, Nashville, Tennessee
37208-3599 and the Department of Biochemistry, Case Western Reserve
University School of Medicine, Cleveland, Ohio 44106-4935.
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